IN THE SPECIFICATION:

On page 3, line 29 through page 4, line 7, please replace with the following paragraph:

Mature human lactadherin is a 364 amino acid protein. Furthermore, lactadherin is a secreted protein and comprises a secretion signal. SEQ ID NO:1 represents the nucleotide ~~amino acid~~ sequence of human lactadherin. Residues 1 to 23 (underlined) represent the secretion signal, and residues 24-387 represent the primary structure of the mature, secreted protein. The murine, bovine and porcine lactadherin have also been identified, isolated and sequenced (see for instance Stubbs et al., PNAS 87 (1990) 8417 ; Hvarregaard et al., Eur. J. Biochem. 240 (1996) 628). The polynucleotide sequence of the murine lactadherin is also represented on SEQID NO:3. Corresponding a~~A~~mino acid residues 1-22 represent the secretion signal, and residues 23-463 represent the primary structure of the mature, secreted protein. Residues 111-147 are deleted in splicing variants of murine lactadherin.

On page 5, lines 18-30, please replace with the following paragraph:

Within the context of the present invention, lactadherin means a protein of mammalian origin, expressed at the surface of milk fat globules, and comprising a RGD site and a domain homologous to the factor VIII C-terminal region (i.e., a factor VIII-like domain). More specifically, the protein is of human, bovine, murine or porcine origin, more preferably of human origin. In a particular embodiment, lactadherin means human lactadherin encoded by ~~having~~ the sequence of SEQ ID NO: 1 or any functional analogs thereof. The term functional analogs designates natural analogs, resulting for instance from the polymorphism or from post-

translational modifications, in particular from splicing(s) or single amino acid deletion, substitution or addition, with reference to the polypeptide encoded by SEQ ID NO: 1, and which retain at least one functional property of human lactadherin. Functional analogs also include lactadherin of other species, in particular murine lactadherin encoded by ~~of~~ SEQ ID NO:3.

On page 7, lines 4-29, please replace with the following paragraphs:

Variants lacking a functional PL binding site are essentially incapable of efficiently binding phospholipids such as phosphatidyl serine. Such variants however, may retain a functional integrin binding site and thus behave as competitors of natural lactadherin. Variants lacking a functional PL (i.e., phosphatidyl serine) binding site can be obtained by different methods. In a particular embodiment, said variants lack all or part of the phosphatidyl serine (PS) binding site. In another particular embodiment, such variants comprise a mutated PS binding site. Of course, variants of this invention can also comprise both deletion and mutation in the PS binding site. The phosphatidyl serine binding site of lactadherin essentially lies in the C-terminal amino acid residues of lactadherin, more particularly in the 150 C-terminal amino acid residues. A variant according to this invention is therefore any variant of lactadherin having a mutation and/or a deletion in/of the 150 C-terminal amino acid residues, and essentially incapable of binding phosphatidyl serine. A more preferred variant is a polypeptide comprising the sequence encoded by ~~of~~ SEQ ID NO:1, said sequence further comprising a mutation and/or a deletion in any one of amino acid residues 242 to 387.

In a particular embodiment of this invention, the variant comprises a deletion of at least 5, preferably at least 10, even more preferably at least 20 contiguous amino acids of the above C-

terminal region. In a particular embodiment, the deletion encompasses the entire 150 C-terminal amino acid residues, more preferably the amino acid residues 242 to 387 encoded by ~~of~~ SEQ ID NO:1. Another specific embodiment of this invention is a lactadherin lacking the 25 C-terminal amino acids, in particular a polypeptide comprising amino acid residues 24-363 of the polypeptide encoded by SEQ ID NO: 1 or a polypeptide comprising amino acid residues 23-439 of the polypeptide encoded by SEQ ID NO:3.

On page 8, line 14 through page 9, line 4, please replace with the following paragraphs:

Variants of lactadherin lacking a functional integrin binding site are essentially incapable of binding efficiently dendritic cells. Such polypeptides can be any variant of lactadherin lacking all or part of the integrin binding site or which comprise a mutated integrin binding site. The integrin binding site of lactadherin essentially resides in an RGD motif located in the N-terminal part of the molecule. For instance, the integrin binding site of human lactadherin encoded by ~~of~~ SEO ID NO:1 lies in residues 46-48 and the integrin binding site of murine lactadherin of SEQ ID NO:4 lies in residues 87-89. The invention therefore resides, in any lactadherin comprising a mutation in and/or a deletion in or of the RGD motif, and which is essentially incapable of binding dendritic cells. Particular examples of such variants are polypeptides encoded by ~~of~~ SEQ ID NO:1 which lack one, two or all of the amino acid residues RGD at position 46-48, and polypeptides of SEQ ID NO:4 which lack one, two or all of the amino acid residues RGD at position 87-89.

Such variants can be used for instance to interfere with the cross-priming of antigens, in vitro, ex vivo or in vivo, by competing with naturally occurring lactadherin for the binding to

particulate antigens. Other types of inhibitors are represented by polypeptides comprising essentially the phospholipid binding site of lactadherin, for instance peptides comprising essentially the amino acid residues 364-385 the polypeptide encoded by ~~of~~ SEQ ID NO:1, or variants thereof. Other inhibitors are represented by antibodies specific for lactadherin, in particular for lactadherin PL or integrin binding sites. Such antibodies (either polyclonals or monoclonals) can be raised by immunisation of an animal using corresponding peptides, and used to reduce an immune reaction.

On page 25, lines 15-22, please replace with the following paragraphs:

- CEEISQEVRGDVFPSY (residues 38 to 53 of the polypeptide encoded by SEQ ID NO: 1) for the RGD domain of human lactadherin. This peptide was used to produce serum B.

- a mixture of three peptides homologous in mouse and human lactadherin CEYLKTFKVAYSLLDG (residues 153 to 166 of the polypeptide encoded by SEQ ID NO: 1), CVTGIITQGARDFG (residues 299 to 311 of the polypeptide encoded by SEQ ID NO: 1) and 20 LPVS TLRL (residues 370 to 387 of the polypeptide encoded by SEQ ID NO: 1). These peptides were used to produce serum C.

On page 26, line 31 through page 28, line 4, please replace with the following paragraphs:

A nucleic acid construct is provided comprising the sequence encoding human lactadherin as depicted in SEQ ID NO: 1 or at least amino acid residues 24-387 of said sequence, corresponding to the mature protein. Such a sequence is represented on SEQ ID NO:2, for instance. Obviously, variants of said sequence can also be used as the starting material. Such a

construct, generally a plasmid, is replicated in a competent host cell, in order to produce suitable quantities of nucleic acid. The nucleic acid is then treated in order to render non-functional the integrin binding site of lactadherin for which it codes. In this respect, the integrin binding site lies essentially in the N-terminal part of the protein, more particularly in the amino acid residues Arg Gly Asp at position 46-48 of the polypeptide encoded by SEQ ID NO:1.

In a particular example, the nucleic acid is treated by deletion of all or part of the sequence encoding amino acid residues 1 to 100 of SEQ ID NO:1, said deletion rendering the protein incapable of binding integrin $\alpha v\beta 5$. Even more preferably, the nucleic acid is treated by deletion of all or part of the sequence encoding amino acid residues 1 to 100 of the polypeptide encoded by SEQ ID NO: 1, said deletion comprising at least all or part of the sequence encoding the amino acid residues Arg Gly Asp at position 46-48 of the polypeptide encoded by SEQ ID NO:1. Preferred examples of variants comprise a deletion of amino acid residues 46-48, 45-49, 40-50 or 35-55 of the polypeptide encoded by SEQ ID NO:1, optionally in combination with a deletion of the amino acid residues 1-23 representing the secretion signal. The deletion can be performed by various means. In particular, the deletion is performed by treatment of the nucleic acid with a restriction enzyme which cleaves said nucleic acid in the appropriate region (including at artificially created restriction sites), optionally followed by digestion of the fragments with exonucleases andlor ligation of the resulting fragments.

In another particular example, the nucleic acid is treated by mutation(s) in all or part of the sequence encoding amino acid residues 1 to 100 of the polypeptide encoded by SEQ ID NO:1, said mutation(s) rendering the protein incapable of binding integrin $\alpha v\beta 5$. Even more preferably, the nucleic acid is treated by mutation(s) in all or part of the sequence encoding

amino acid residues 1 to 100 of the polypeptide encoded by SEQ ID NO:1, said part comprising at least all or part of the sequence encoding the amino acid residues Arg Gly Asp at position 46-48 of the polypeptide encoded by SEQ ID NO:1. Preferred examples of variants comprise at least a mutation of one amino acid selected from the amino acid residues Arg Gly Asp at position 46-48 of the polypeptide encoded by SEQ ID NO:1. The mutation can be carded out by various means, including site-directed mutagenesis, amplification with mutated primers, nucleic acid synthesis and cloning, etc. The mutation can lead to the suppression of one single amino acid residue or to its replacement by another conservative or non-conservative amino acid residue.

On page 28, lines 9-19, please replace with the following paragraphs:

Particular variants of the present invention are:

- a protein comprising amino acid residues 49-387 of the polypeptide encoded by SEQ ID NO:1;
- a protein of SEQ ID NO:1 with a deletion of amino acid residues 46-48;
- a protein encoded by ~~of~~ SEQ ID NO:1 with a deletion of amino acid residues 1-23 and 46-48;
- a protein comprising amino acids 23-387 of the polypeptide encoded by SEQ ID NO:1 with a mutation in amino acid residue Arg at position 46;
- a protein comprising amino acids 23-387 of the polypeptide encoded by SEQ ID NO:1 with a mutation in amino acid residue Gly at position 47;
- a protein comprising amino acids 23-387 of the polypeptide encoded by SEQ ID NO:1 with a mutation in amino acid residue Asp at position 48;

On page 29, lines 6-28, please replace with the following paragraphs:

A nucleic acid construct is provided comprising the sequence encoding human lactadherin as depicted in SEQ ID NO: 1, as disclosed in example 4. The nucleic acid is then treated in order to render non-functional the PS binding site of lactadherin for which it codes. In this respect, the PS binding site lies essentially in the C-terminal part of the protein, more particularly in the amino acid residues 242 to 387 of the polypeptide encoded by SEQ ID NO:1, even more preferably in the amino acid residues 350-387 of the polypeptide encoded by SEQ ID NO:1.

In a particular example, the nucleic acid is treated by deletion of all or part of the sequence encoding amino acid residues 242 to 387 of the polypeptide encoded by SEQ ID NO:1, more preferably comprising at least the amino acid residues 360-387 of the polypeptide encoded by SEQ ID NO:1, said deletion rendering the protein incapable of binding PS. The deletion can be performed by various means. in particular, the deletion is performed by treatment of the nucleic acid with a restriction enzyme which cleaves said nucleic acid in the appropriate region (including at artificially created restriction sites), optionally followed by digestion of the fragments with exonucleases and/or ligation of the resulting fragments.

In another particular example, the nucleic acid is treated by mutation(s) in all or part of the sequence encoding amino acid residues 242 to 387 of the polypeptide encoded by SEQ ID NO:1, more preferably at least in the sequence encoding the amino acid. residues 360-387 of the polypeptide encoded bySEQ ID NO:1, said mutation(s) rendering the protein incapable of binding PS. The mutation can be carried out by various means, including site-directed mutagenesis, amplification with mutated primers, nucleic acid synthesis and cloning, etc.

On page 29, line 33 through page 30, line 6, please replace with the following paragraphs:

Particular variants of the present invention are:

- a protein comprising amino acid residues 1 to 242 of the polypeptide encoded by SEQ ID NO:1;

- a protein comprising amino acid residues 24 to 242 of the polypeptide encoded by SEQ ID NO: 1;

- a protein encoded by ~~of~~ SEQ ID NO:1 with a deletion of amino acid residues 360-387;

- a protein of encoded by ~~of~~ SEQ ID NO:1 with a mutation in one or several amino acid residues of the sequence 360-387.